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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,647	11/27/2001	Bernd Riedl	BAYER 18A	1010

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	
MAIL DATE	**DELIVERY MODE**
03/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,647	RIEDL ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74,81,87,93,100-104,106-109,111-115 and 117-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74,81,87,93,100-103,106-109,111-114 and 117* is/are rejected.

7)☒ Claim(s) *104, 115, 118, 119* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 28, 2008 has been entered.

Claims 74, 81, 87, 93, 100-104, 106-109, 111-115 and 117-119 are currently pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claims 74, 81, 87, 93, 100-103, 106-109, 111-114 and 117 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the

treatment of carcinoma of the colon or villous colon adenoma (based on the *in vitro* treatment of the tumor cell lines HCT116 and DLD-1 provided in the specification), does not reasonably provide enablement for a method for the treatment of all types of solid tumors, carcinomas, myeloid disorders or adenomas; or a method for inhibiting RAF-kinase in a human or mammal. The reasons of the previous office action(s) are incorporated here by reference. The following Wands analysis is provided supplementing the reasons already provided in the previous office action(s).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating solid tumors, carcinomas, myeloid disorders, and adenomas. Further, a method for inhibiting RAF-kinase in a human or mammal by administering the compounds.

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat all types of solid tumors, carcinomas, myeloid disorders, and adenomas. As illustrative of the state of the art, Gura et al. (Science 1997) and Johnson et al., (British J. of Cancer 2001) are provided.

Gura et al., cited for evidentiary purposes, teaches that researchers face the problem of sifting through potential anticancer agents to find the ones promising enough to make human clinical trials worthwhile and further teach that since formal screening began in 1955, many

thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (see the first two paragraphs). It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. With regard to unpredictability, Johnson et al., cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. These state of the art references plainly demonstrate that the art of developing and testing anticancer drugs particularly for use in humans is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present to direct one to protect a potential host from the disorders embraced by the instant claims nor there are doses given for the treatment of the disorders recited. The specification provides assays (see pages 94-96) to test the compounds *in vitro* and discloses that the compounds exhibit raf kinase inhibitory properties. However, no *in vivo* test procedures or data provided for the compounds commensurate in scope of the claims and there is no disclosure regarding how the *in vitro* results correlate to *in vivo* tests. *In vivo* test procedures

are provided for the cancers of the colon in mice (see page 96), however, there is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims.

6) The breadth of the claims: The instant claims embrace the treatment of solid tumors, carcinomas, myeloid disorders, and adenomas and further, a method of inhibiting RAF-kinase in a human or mammal. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Response to arguments

Applicant's arguments have been fully considered but they have not been found to be persuasive. The references relied upon by the applicant (i.e., Awada (2005); Clark (2005); Moore (2005); Escudier (2007); etc.) are not state of the art references as of the filing date of the instant application. Applicant has not provided any reference(s) that forms sufficient evidence that claimed uses were art-recognized based on activity relied on at the time of applicants' effective filing date. MPEP 2164.05(a). As explained in the previous office action, the state of the art is not indicative of the fact that treatments of all types of diseases encompassed by the instant claims are conventional or well known.

Applicant relies on the state of the art references, Kolch and Monia and argues that 'the references teach correlation of raf inhibition with the inhibition of the growth of a variety of

tumor types'. Contrary to applicant's arguments, the state of the art references Kolch and/or Monia do not establish a therapeutic method for the treatment of all types of solid tumors, carcinomas, myeloid disorders or adenomas generally. As explained in the previous office action, the state of the art is not indicative of the fact that treatments of all types of diseases encompassed by the instant claims are conventional or well known. The cited references are too speculative and invite further research into treatment of cancer diseases. For example, Monia at page 668 provides that "the emergence of novel therapies that specifically reverse the oncogenic effect of these gene products has generally been slow". All references provided as evidence of enabling disclosure present no evidence that the claimed compounds actually have activity in treating all types of solid tumor, carcinoma, myeloid disorders or adenoma. There is no evidence of record that the claimed compounds are actually efficacious in treating all types of solid tumor, carcinoma, myeloid disorders or adenoma; or inhibit RAF-kinase generally.

Applicant's arguments based on the state of the art references – Monia, Kolch, Daum, Fridman, etc. have been fully considered but not deemed to be persuasive. However, the cited references do not cure the deficiencies of the specification. Considered separately or together, these references invite further research into the treatment of solid tumor, carcinoma, myeloid disorder, adenoma, etc. through inhibition of RAF-kinase.

Applicant argues that 'Using the claimed compounds would be routine for those skilled in the art in view of applicant's disclosure, as is shown by the various studies made of record'. The guidance in the specification is limited to an *in vitro* cell proliferation assay showing inhibition of two colon cancer cell lines; and summary instructions relating to an *in vivo* assay in mice that can be performed to determine the inhibition of a human colon adenocarcinoma cell

line (see pages 94-96). There is no evidence of record how the provided data is directly involved in the pathogenesis of all types of solid tumors, carcinoma, myeloid disorders or adenoma and/or that simply inhibiting RAF-kinase will lead to treatment of all of these diseases. It is not routine for one skilled in the art to synthesize, purify, screen for RAF-kinase inhibition, and test for anticancer activity of the claimed compounds.

Applicant argues that 'claim 117 is directed to a method of inhibiting raf-kinase in a human or other mammal and not a method of treatment claim for any condition, including cancer'. As previously provided, the claim is directed towards 'a method for inhibiting RAF-kinase in a human or mammal' - which involves administering of the compound to human or mammal and therefore reaches through to the treatment of all types of diseases associated with RAF-kinase. The findings and conclusions in the cited publications are with respect to inhibition of RAF kinase and the application of such activity for specific types of cancerous growth. The development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single therapeutic approach. The evidence of record does not disclose any known compounds of similar structure, which have been demonstrated to inhibit RAF-kinase generally and thereby treat all diseases mediated by raf kinase; or treat all types of solid tumors,

carcinomas, myeloid disorders or adenomas, when the compounds are administered to a human or a mammal.

Allowable Subject Matter

Claims 104, 115, 118 and 119 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

March 18, 2009